

# **Autoimmunity in Obsessive-Compulsive Disorder and tic disorders**

## **Auto-imunidade em Transtorno Obsessivo- Compulsivo e transtornos de tiques**

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS) has sparked spirited debate among researchers, clinicians and academics. Based on the association between GAS infections and the acute onset or exacerbation of OCD and tics in the pediatric population, the PANDAS concept grew out of the post World War II resurgence of rheumatic fever (RF) and Sydenham's chorea (SC). A major manifestation of RF, SC is believed to occur secondary to autoantibodies that are directed against Group A streptococcus (GAS) but cross-react with epitopes on basal ganglia neurons causing motoric and behavioral disturbances. Historic and recent research has suggested that OCD and tics are more prevalent in SC patients than in the general population. This higher prevalence of OCD in patients with SC may parallel some cases of acute onset pediatric OCD that could be due to GAS as well. Diagnostic criteria for PANDAS include pediatric onset, presence of OCD and/or tics, episodic course, neurological abnormalities, and an association with GAS infection.<sup>1</sup>

The high prevalence of OCD symptoms in patients with SC has prompted an exploration of a potential autoimmune basis for OCD in a subset of patients. Studies have demonstrated the high prevalence of OCD in patients with other autoimmune diseases, such as systemic lupus erythematosus, myasthenia gravis, and multiple sclerosis. Conversely, a chart review study concluded that adult patients with OCD appeared to have an increased rate of immune-related diseases beyond that seen in other psychiatric disorders.<sup>2</sup>

GAS is a common pathogen in the pediatric population with a wide spectrum of clinical manifestations. PANDAS could be considered as a broadening of SC, or this subtype of OCD/TS may yet have a unique pathophysiology distinct from SC. An association between an exacerbation of OCD or tic symptoms and elevated GAS titers or documented streptococcal infections has been demonstrated in several studies. A pediatric group examined all children for GAS who presented with a sudden onset of a neuropsychiatric problem such as OCD, a tic disorder, or late age-onset ADHD, and found that the neuropsychiatric symptoms rapidly remitted with antibiotic therapy.<sup>3</sup>

In the last decade, a greater degree of allelic and clinical diversity has been appreciated with respect to GAS infections. To date, over 80 serotypes of GAS have been described, with 150 alleles of the M protein, 89 alleles of speB, and 269 alleles of the Sic protein known to exist. In fact, 16 of the 44 known GAS proteins have been found to be immunogenic. Some of these suspected virulence factors were not present in earlier strains of GAS<sup>4</sup> – possibly due to the fact the GAS genome randomly reassorts over time, increasing the chance of new virulence factors developing. Clinical evidence that GAS may be changing is reflected in changes in the clinical manifestations of illnesses caused by GAS. In the outbreaks of RF in the mid-1980s, a higher representation of certain serotypes and mucoid strains of

GAS was noted, and a large proportion of individuals had only mild or no history of prior pharyngitis. Recent reports suggest that the incidence of scarlet fever and necrotizing fasciitis has increased dramatically in the past few decades.

Epidemiological studies indicate that the same streptococcal strain to cause infection of varying severity in different individuals, suggesting that host factors play an important role in determining the morbidity of GAS infections. Patients with a propensity to produce high levels of proinflammatory cytokines in response to GAS products are noted to exhibit severe clinical manifestations. Young age at time of streptococcal infection may alter future immune responses to group A streptococcus. After streptococcal infections, titers may remain elevated for six months to a year. Murphy et al. found that those with a dramatically fluctuating neuropsychiatric symptom course had more evidence of persistent elevations in one or more strep titers compared to those that had a course inconsistent with PANDAS.<sup>5</sup> This finding may be due to the relative proximity of the streptococcal infection and repeated streptococcal exposures leading to more severe and turbulent symptoms. Persistent immune activation to GAS also may be a consequence of multiple factors including developmental, genetic, and/or environmental influences.

Potential mechanisms by which autoantibodies cause clinical manifestations in CNS diseases such as SC and PANDAS include direct stimulation or blockade of receptors in the basal ganglia, or immune complexes promoting inflammation of these brain regions. New research supports antibody-mediated neuronal cell signaling in the pathogenesis of SC. Monoclonal antibodies in SC patients that were targeted to N-acetyl-beta-D-glucosamine – the dominant epitope of GAS – were noted to show specificity to mammalian lysoganglioside GM1, a CNS ganglioside that influences neuronal signal transduction.<sup>6</sup> Sera from SC patients further contained antibodies that targeted human neuronal cells and specifically induced calcium/calmodulin-dependent protein (CaM) kinase II activity, while sera from patients convalescing or from patients with other streptococcal-related diseases lacked activation of this kinase. The binding of autoantibodies to these neuronal cell surface antigens may promote signal transduction, leading to the release of excitatory neurotransmitters. The potential mechanism by which symptoms occur in SC may also explain the pathogenesis of PANDAS.

Systemic autoantibodies would need to traverse the blood brain barrier (BBB) and gain access to the CNS. The exact mechanism is not known, however, a variety of mechanisms have been proposed. Inflammatory toxins may lead to a breakdown of the BBB. Cytokines can cross the BBB via the circumventricular organs, and when infused peripherally are known to activate inflammatory cells on the CNS side of the BBB. Peripheral B cells that are cross-reactive to a CNS epitope also have been shown to induce intrathecal production of antibody. Therefore, the induction of intrathecal antibodies by peripheral B cells, activation of CNS inflammatory cells by peripheral cytokines, and the traversing of the BBB by peripheral B cells and antibodies are all viable explanations by which autoantibodies produced in response to a peripheral antigen are able to react with neural structures.

A definitive association has yet to be established, but accumulating support exists for the association of an autoimmune response to streptococcus and the onset or exacerbation of OCD symptoms/tics. Additional research is needed to confirm the role of GAS infections and other immune-based triggers (along with genetic and environmental triggers) in the onset of neuropsychiatric illnesses that may then lead to immune specific therapies.

**Tanya K Murphy and David S Husted**  
Department of Psychiatry, University of Florida,  
Gainesville, FL

## References

1. Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998;159(2):264-71. Commented in: *Am J Psychiatry*. 2002;159(2):320.
2. Dinn WM, Harris CL, McGonigal KM, Raynard RC. Obsessive-compulsive disorder and immunocompetence. *Int J Psychiatry Med*. 2001;31(3):311-20.
3. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med*. 2002;156(4):356-61.
4. Goldmann O, Chhatwal GS, Medina E. Immune mechanisms underlying host susceptibility to infection with group A streptococci. *J Infect Dis*. 2003;187(5):854-61.
5. Murphy TK, Sajid M, Soto O, Shapira N, Edge P, Yang M, et al. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. *Biol Psychiatry*. 2004;55(1):61-8.
6. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nat Med*. 2003;9(7):914-20. Commented in: *Nat Med*. 2003;9(7):823-5.